PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

4/8

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* 21 JULY 2005 see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/GB2005/000174	International filing date *(day/month/year)* 19.01.2005 / Priority date *(day/month/year)* 21.01.2004
International Patent Classification (IPC) or both national classification and IPC A61K9/16	
Applicant THE SCHOOL OF PHARMACY	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Marttin, E

Telephone No. +31 70 340-2862

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000174

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000174

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19, with regard to industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 19, with regard to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000174

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13
	No:	Claims	1-12,14-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1
Reference is made to the following documents:

D1 : US 2002/076444 A1 (DI COSTANZO FRANCIS ET AL) 20 June 2002 (2002-06-20)

D2 : JAMEELA S R ET AL: "Progesterone-loaded chitosan microspheres: a long acting biodegradable controlled delivery system" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 52, no. 1-2, 2 March 1998 (1998-03-02), pages 17-24, XP004113650 ISSN: 0168-3659

D3 : PRADHAN R S ET AL: "FORMULATION AND IN VITRO RELEASE STUDY ON POLY (DL-LACTIDE) MICROSPHERES CONTAINING HYDROPHILIC COMPOUNDS: GLYCINE HOMOPEPTIDES" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 30, no. 2, 1 May 1994 (1994-05-01), pages 143-154, XP000451918 ISSN: 0168-3659

D4 : MATEOVIC T ET AL: "Influence of different droplet stabilizers on the properties of microspheres prepared by the solvent evaporation method" ACTA TECHNOLOGIAE ET LEGIS MEDICAMENTI, vol. 14, 2003, pages 53-66, XP008049338 cited in the application

Document D1 discloses (for relevant passages see Search Report): a process for producing microparticles comprising adding Eudragit S100, ketoprofen and the surfactant Crodesta F-70 (HLB=7) to ethanol, followed by emulsifying the organic phase into an aqueous phase, which contains Span 60 (HLB=4.7), followed by filtration under vacuum and drying, resulting in evaporation of the solvent.

2.1
INDEPENDENT CLAIM 1

As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

2.2
INDEPENDENT CLAIM 18

As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 18. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

2.3
INDEPENDENT CLAIM 19

As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 19. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

3
Document D2 discloses (for relevant passages see Search Report): a process for making particles comprising mixing a progesterone with a solution of chitosan in acetic acid and

dispersing this mixture in liquid paraffin and sorbitan sesquioleate. The dispersion is emulsified, and after centrifugation the microparticles are vacuum dried, which results in solvent evaporation. The particle size distribution is 67% of the particles between 45-90 µm and 20% between 90-150 µm.

3.1
INDEPENDENT CLAIM 1

As can be seen from the above, document D2 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

3.2
INDEPENDENT CLAIM 18

As can be seen from the above, document D2 discloses in combination all the features defined in independent claim 18. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

3.3
INDEPENDENT CLAIM 19

As can be seen from the above, document D2 discloses in combination all the features defined in independent claim 19. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

4
Document D3 discloses (for relevant passages see Search Report): a process for the production of microspheres comprising emulsifying a suspension of glycine homopeptide, poly-DL-lactide and acetone in mineral oil with sorbitan sesquioleate followed by evaporation of the acetone. The major fraction of the microparticles was in the range of

38-125 µm.

4.1
INDEPENDENT CLAIM 1

As can be seen from the above, document D3 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

4.2
INDEPENDENT CLAIM 18

As can be seen from the above, document D3 discloses in combination all the features defined in independent claim 18. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

4.3
INDEPENDENT CLAIM 19

As can be seen from the above, document D3 discloses in combination all the features defined in independent claim 19. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

5
INVENTIVE STEP

5.1
All embodiments covered by the claims, particularly by the independent claims, should satisfy the criteria of inventive step (Article 33(3) PCT). The inventive step being based on the achievement of a technical effect, namely that microparticles having a

median diameter of up to 100 µm can be produced by means of the method. It must therefore be credible that all the alternatives claimed must be a solution to the problem, namely to produce microparticles having a median diameter of up to 100 µm.
It is clear that the technical features of a present claims 1, 18 and 19 in view of the description (see example 18, page 19, lines 6-8) cannot lead to the production of microparticles having this diameter, since PVAP microparticles are likely to be too large to fall within the terms the invention and therefore cannot solve the problem of the present application.

Moreover, in view of document D4 it is clear that the technical features of present claims 1, 18 and 19 cannot lead to the production of microparticles having a median diameter of up to 100 µm. Document D4 discloses (for relevant passages see Search Report): a method for producing particles comprising mixing a dispersion of Eudragit RS, pipedimic acid and Span 20 in acetone with paraffin containing Span 80 to form an emulsion followed by evaporation to obtain microspheres having geometric mean diameters above 100 µm, namely 266-361 µm (see D4: table 1). Additionally, in view of the description of the present application page 3, line 26 - page 4, line 1 the microparticles produced by the method of D4 also do not function as intended.

Thus, the subject-matter of claims 1-19 can not be considered inventive (Article 33(3) PCT) .

6
DEPENDENT CLAIMS 2-17

Dependent claims 2-17 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

7
For the assessment of the present claim 19 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can

also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

10597328

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

4/8

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* 21 JULY 2005 see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/GB2005/000174	International filing date *(day/month/year)* 19.01.2005
	Priority date *(day/month/year)* 21.01.2004
International Patent Classification (IPC) or both national classification and IPC A61K9/16	
Applicant THE SCHOOL OF PHARMACY	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Marttin, E

Telephone No. +31 70 340-2862

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000174

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000174

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19, with regard to industrial applicability

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 19, with regard to industrial applicability

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2005/000174

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	13
	No:	Claims	1-12,14-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claim 19 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1
Reference is made to the following documents:

D1 : US 2002/076444 A1 (DI COSTANZO FRANCIS ET AL) 20 June 2002 (2002-06-20)

D2 : JAMEELA S R ET AL: "Progesterone-loaded chitosan microspheres: a long acting biodegradable controlled delivery system" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 52, no. 1-2, 2 March 1998 (1998-03-02), pages 17-24, XP004113650 ISSN: 0168-3659

D3 : PRADHAN R S ET AL: "FORMULATION AND IN VITRO RELEASE STUDY ON POLY (DL-LACTIDE) MICROSPHERES CONTAINING HYDROPHILIC COMPOUNDS: GLYCINE HOMOPEPTIDES" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 30, no. 2, 1 May 1994 (1994-05-01), pages 143-154, XP000451918 ISSN: 0168-3659

D4 : MATEOVIC T ET AL: "Influence of different droplet stabilizers on the properties of microspheres prepared by the solvent evaporation method" ACTA TECHNOLOGIAE ET LEGIS MEDICAMENTI, vol. 14, 2003, pages 53-66, XP008049338 cited in the application

2

Document D1 discloses (for relevant passages see Search Report): a process for producing microparticles comprising adding Eudragit S100, ketoprofen and the surfactant Crodesta F-70 (HLB=7) to ethanol, followed by emulsifying the organic phase into an aqueous phase, which contains Span 60 (HLB=4.7), followed by filtration under vacuum and drying, resulting in evaporation of the solvent.

2.1
INDEPENDENT CLAIM 1

As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

2.2
INDEPENDENT CLAIM 18

As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 18. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

2.3
INDEPENDENT CLAIM 19

As can be seen from the above, document D1 discloses in combination all the features defined in independent claim 19. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

3
Document D2 discloses (for relevant passages see Search Report): a process for making particles comprising mixing a progesterone with a solution of chitosan in acetic acid and

dispersing this mixture in liquid paraffin and sorbitan sesquioleate. The dispersion is emulsified, and after centrifugation the microparticles are vacuum dried, which results in solvent evaporation. The particle size distribution is 67% of the particles between 45-90 µm and 20% between 90-150 µm.

3.1
INDEPENDENT CLAIM 1

As can be seen from the above, document D2 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

3.2
INDEPENDENT CLAIM 18

As can be seen from the above, document D2 discloses in combination all the features defined in independent claim 18. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

3.3
INDEPENDENT CLAIM 19

As can be seen from the above, document D2 discloses in combination all the features defined in independent claim 19. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

4
Document D3 discloses (for relevant passages see Search Report): a process for the production of microspheres comprising emulsifying a suspension of glycine homopeptide, poly-DL-lactide and acetone in mineral oil with sorbitan sesquioleate followed by evaporation of the acetone. The major fraction of the microparticles was in the range of

38-125 µm.

4.1
INDEPENDENT CLAIM 1

As can be seen from the above, document D3 discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

4.2
INDEPENDENT CLAIM 18

As can be seen from the above, document D3 discloses in combination all the features defined in independent claim 18. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

4.3
INDEPENDENT CLAIM 19

As can be seen from the above, document D3 discloses in combination all the features defined in independent claim 19. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

5
INVENTIVE STEP

5.1
All embodiments covered by the claims, particularly by the independent claims, should satisfy the criteria of inventive step (Article 33(3) PCT). The inventive step being based on the achievement of a technical effect, namely that microparticles having a

median diameter of up to 100 µm can be produced by means of the method. It must therefore be credible that all the alternatives claimed must be a solution to the problem, namely to produce microparticles having a median diameter of up to 100 µm.
It is clear that the technical features of a present claims 1, 18 and 19 in view of the description (see example 18, page 19, lines 6-8) cannot lead to the production of microparticles having this diameter, since PVAP microparticles are likely to be too large to fall within the terms the invention and therefore cannot solve the problem of the present application.

Moreover, in view of document D4 it is clear that the technical features of present claims 1, 18 and 19 cannot lead to the production of microparticles having a median diameter of up to 100 µm. Document D4 discloses (for relevant passages see Search Report): a method for producing particles comprising mixing a dispersion of Eudragit RS, pipedimic acid and Span 20 in acetone with paraffin containing Span 80 to form an emulsion followed by evaporation to obtain microspheres having geometric mean diameters above 100 µm, namely 266-361 µm (see D4: table 1). Additionally, in view of the description of the present application page 3, line 26 - page 4, line 1 the microparticles produced by the method of D4 also do not function as intended.

Thus, the subject-matter of claims 1-19 can not be considered inventive (Article 33(3) PCT) .

6
DEPENDENT CLAIMS 2-17

Dependent claims 2-17 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

7
For the assessment of the present claim 19 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can

also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for the manufacture for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.